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Gefitinib (IRESSA) with Vinorelbine or Vinorelbine/Cisplatin for Chemotherapy-Naive Non-small Cell Lung Cancer Patients

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This phase I study assessed the safety, pharmacokinetics, and efficacy of gefitinib (IRESSA) combined with vinorelbine or vinorelbine/cisplatin in chemotherapy-naive patients with advanced non-small cell lung cancer (NSCLC). Patients received gefitinib 250 mg/day and vinorelbine (group A; $n = 6$) or vinorelbine/cisplatin (group B; $n = 8$). An additional set of group B patients ($n = 9$) received gefitinib 500 mg/day with vinorelbine/cisplatin. Adverse events were consistent with individual treatments of gefitinib (mild reversible rash, diarrhea) and chemotherapy (asthenia, fever, nausea, vomiting, constipation), although there was a higher than expected incidence of Common Toxicity Criteria grade 3 or 4 hematologic adverse events, specifically febrile neutropenia and neutropenia. Pharmacokinetic data suggested that neither of the chemotherapy regimens affected steady-state exposure to gefitinib and also that steady-state gefitinib did not alter exposure to vinorelbine or cisplatin. Objective, durable antitumor activity was observed: five partial responses (one in group A; four in group B) and six patients with stable disease (all in group B). The safety data demonstrated that gefitinib with vinorelbine or vinorelbine/cisplatin resulted in severe myelosuppression leading to an unacceptable rate of febrile neutropenia. This study does not support the concurrent administration of gefitinib and vinorelbine, with or without cisplatin, as a valid treatment for advanced NSCLC.

Key Words: Gefitinib, Vinorelbine, Cisplatin, Non-small cell lung cancer, Chemotherapy naive, Safety

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Lung cancer is currently the most lethal tumor type in Western countries, accounting for approximately 1 million deaths annually, with an estimated 1.32 million people newly diagnosed with the disease each year.[1] Among the different histologic types, non-small cell lung cancer (NSCLC) remains an important challenge for medical oncology because most patients are diagnosed at an advanced stage of disease.

Most patients with advanced NSCLC (stage IV or IIIB with pleural or pericardial malignant effusion) are not eligible for surgery or radiotherapy. However, chemotherapy is currently the standard treatment option for patients able to tolerate aggressive therapy.[2] Studies reporting data for chemotherapy for inoperable stage IIIB/IV disease show a median survival of only approximately 8 months, a 1-year survival rate of 35%, and 5-year survival rate of <5%.[3,4] Platinum-based combinations have been accepted as a standard for the treatment of advanced or metastatic NSCLC, based on the results of phase III randomized trials and the meta-analysis by the NSCLC Collaborative Group published in 1995.[4,5] However, better treatment strategies are badly needed, and the investigation of combinations of novel agents with chemotherapy for first-line treatment is of great interest.

Gefitinib (IRESSA), an anilinoquinazoline, is an orally active inhibitor of epidermal growth factor receptor tyrosine kinase, an enzyme that catalyzes phosphorylation reactions implicated in the proliferation and survival of cancer cells via intracellular signal transduction pathways. In phase II trials of gefitinib monotherapy in patients with previously treated, locally advanced or metastatic NSCLC, gefitinib 250 mg/day demonstrated clinically significant antitumor activity as evidenced by durable tumor responses (objective response rate, 12%–18%), disease control (rate, 42%–54%), and improvement in disease-related symptoms in 40% to 43% of patients.[6,7] Adverse events (AEs) consisted predominantly of mild (grades 1–2) diarrhea and skin reactions. The dose of gefitinib 500 mg/day produced a higher frequency of AEs but did not increase efficacy.[6,7]

The potential for combining gefitinib and chemotherapy, which have largely nonoverlapping toxicity profiles, has been shown in preclinical studies in which the antitumor activity of gefitinib was enhanced when used in combination with a number of cytotoxic drugs.[8,9] Furthermore, data from phase I trials showed that combinations of gefitinib with

carboplatin/paclitaxel in patients with NSCLC and with cisplatin/gemcitabine in patients with advanced metastatic solid tumors showed antitumor activity and were generally well tolerated with no apparent increase in higher grade toxicity.[10] The combination of gefitinib and chemotherapy did not cause an increase in exposure to any of the chemotherapy agents tested, although increased exposure to gefitinib was seen with the carboplatin/paclitaxel regimen. There was no evidence that gefitinib had an antagonistic effect on the efficacy of chemotherapy.[10] In phase III trials in chemotherapy-naive patients with advanced NSCLC, the addition of gefitinib to paclitaxel/carboplatin or gemcitabine/cisplatin gave no added survival benefit.[11,12] However, the combination of gefitinib with vinorelbine/cisplatin in this population has not been reported until now. Single-agent vinorelbine has demonstrated clinical activity in a number of phase I and II studies, with overall response rates in NSCLC patients of 14% to 30% using the standard schedule of 30 mg/m^2 per week.[13] In a prospective, randomized trial to compare vinorelbine and cisplatin with vindesine and cisplatin, improved response rate and survival versus single-agent vinorelbine was seen in the vinorelbine/cisplatin arm: response rates were 30% for vinorelbine/cisplatin versus 19% for vindesine/cisplatin ($p = 0.02$) and 14% for vinorelbine alone ($p < 0.001$). Median survival was 40 weeks in the vinorelbine/cisplatin arm compared with 32 weeks in the vindesine/cisplatin arm and 31 weeks for vinorelbine alone.[14]

The present phase I study was aimed at assessing the safety and pharmacokinetics of gefitinib when used in combination with vinorelbine and cisplatin. Gefitinib is cleared primarily by the hepatic route as parent compound plus metabolites and the major cytochrome P-450 enzyme involved in gefitinib metabolism is CYP3A4.[15] Because the main elimination pathway of vinorelbine is also hepatic metabolism principally mediated by CYP3A4,[16] this raised the limited possibility of a pharmacokinetic interaction.

METHODS

Trial Design

This was an open pilot trial of two doses of gefitinib (250 and 500 mg) in combination with chemotherapy in chemotherapy-naive patients with advanced NSCLC. The primary objective was to assess the safety of gefitinib when used in combination with the cytotoxic agents vinorelbine and cisplatin. Secondary objectives included an assessment of whether exposure to gefitinib, vinorelbine, or vinorelbine/cisplatin was altered when the agents were given in combination and an assessment of antitumor activity.

Patients and Treatment

Patients were chemotherapy naive, had a World Health Organization performance status (PS) of ≤2, were age 18 years and older, had histologically confirmed locally advanced or metastatic NSCLC, and gave written, informed consent. The trial was performed in accordance with the Declaration of Helsinki. Criteria that caused patients to be ineligible for the trial included brain metastasis or spinal cord compression that was newly diagnosed and/or had not yet been definitively treated; radiotherapy <2 weeks previously; other coexisting malignancies or malignancies diagnosed within the past 5 years with the exception of basal cell carcinoma or cervical cancer in situ; weight loss of ≥10% in the past 3 months; absolute neutrophil count of $<2 \times 10^9$ ml^{-1}; white blood cell count of $<4 \times 10^9$ ml^{-1}; and platelet count of $<10^{11}$ ml^{-}.

The trial was run as two groups of patients, group A and group B, with patients allocated at the investigators' discretion. Group A received gefitinib and vinorelbine, and group B received gefitinib in combination with vinorelbine and cisplatin. Initially, patients were assigned to oral gefitinib 250 mg/day. In group A, patients received a standard regimen of vinorelbine (30 mg/m^2 intravenously [IV]), administered on days 1, 8, 15, and 22 of each 28-day cycle and gefitinib daily starting on day 2. Additional cycles of vinorelbine concurrently with gefitinib were administered every 4 weeks for up to six cycles in total. In group B, patients received a standard chemotherapy regimen of cisplatin (80 mg/m^2 IV) and vinorelbine (30 mg/m^2 IV), administered on day 1. Vinorelbine was also administered on day 8 of each 21-day cycle and oral gefitinib daily starting on day 2. Additional cycles of chemotherapy were administered concurrently with gefitinib every 3 weeks for up to six cycles. For both groups, at the end of the combination treatment period, benefiting patients could continue receiving gefitinib monotherapy until disease progression, withdrawal due to unacceptable toxicity, or a patient's unwillingness to continue.

Safety

AEs and laboratory values were graded according to the National Cancer Institute Common Toxicity Criteria (CTC) version 2.0. AEs continued to be recorded for a 30-day follow-up period after the last administration of study treatment. Withdrawn patients who had CTC grade 3 or 4 laboratory values at the time of withdrawal were followed up until the laboratory values returned to CTC grade 1 or until 30 days after the date of withdrawal. Patients were evaluated for safety on day 29 in group A and day 22 in group B. When the first six assessable patients at the gefitinib 250 mg/day dose level in each group had completed this period, a full safety evaluation was performed.

Dose Adjustment

Dose adjustments during a cycle were made based on weekly absolute granulocyte counts and/or platelet counts. Vinorelbine was reduced by 25% in the case of an absolute granulocyte count of $<1.2 \times 10^9$/L and/or platelet count of $<100 \times 10^9$/L. Vinorelbine was withheld in the case of an absolute granulocyte count of $<1 \times 10^9$/L and/or platelet count of $<75 \times 10^9$/L. Dose adjustments for subsequent cycles were made based on the toxicity seen in the previous cycle.

Dose-Limiting Toxicity

Based on the anticipated toxicities of vinorelbine, vinorelbine and cisplatin, and gefitinib monotherapy, an individual drug-related dose-limiting toxicity (DLT) was defined as follows: CTC grade 4 thrombocytopenia with severe

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bleeding or grade 4 neutropenia associated with sepsis requiring hospitalization; grade 3/4 skin toxicity; grade 3/4 gastrointestinal toxicity (diarrhea for >4 days despite aggressive antidiarrheal therapy and temporary or permanent discontinuation of gefitinib); grade 4 gastrointestinal toxicity (nausea or vomiting for >4 days despite aggressive antiemetic therapy and temporary or permanent discontinuation of gefitinib); deterioration of visual acuity or other significant ocular toxicity; grade 3/4 central nervous system, cardiac, lung, or renal toxicity. If there was a higher than expected incidence of drug-related hepatic toxicity, consideration was given to not escalating the dose of trial medication.

After the full safety evaluation after cycle 1, if no more than one patient experienced drug-related DLT among the six assessable patients, the dose was considered safe and the 500-mg dose level was opened to accrual. If two or three patients experienced drug-related DLT among the six assessable patients, this dose level was expanded to obtain 12 assessable patients. If no more than three patients experienced drug-related DLT among these 12 assessable patients, the dose was considered safe in combination and the 500-mg dose level was opened to recruitment. If, however, four or more patients experienced drug-related DLT among these 12 assessable patients, the dose was not considered safe in combination and the 500-mg dose level was not opened to accrual. If four or more patients experienced drug-related DLT among the first six assessable patients, the dose was not considered safe in combination and the 500-mg dose level was not opened to accrual.

Pharmacokinetics

Blood samples for determination of concentrations of vinorelbine, cisplatin, and gefitinib were obtained during the first and second cycles of gefitinib and chemotherapy, with the aim of obtaining satisfactory samples for each agent from at least four patients at each gefitinib dose level. For vinorelbine assessment (groups A and B), a predose sample was taken on day 1, followed by samples at 15 and 30 minutes and 1, 4, 8, and 24 hours after the start of infusion. This was repeated on day 22. For cisplatin (group B), samples were taken on day 1 predose and at 2, 2.5, 3, 4, and 5 hours after infusion start, also repeated on day 22. For gefitinib (groups A and B), samples were taken on day 21 at predose and at 3, 7, and 24 hours and on day 22 at 3, 7, and 24 hours (the day 21 24-hour sample also acting as the day 22 predose sample).

The minimum (trough) steady-state plasma concentration during the 24-hour dosing interval (C_{min}^{ss}) for gefitinib was taken as the concentration in the predose sample collected on the sampling day when given alone or as the concentration in the 24-hour sample collected on the sampling day when given in combination with chemotherapy. The maximum plasma concentration (C_{max}) for vinorelbine and free cisplatin was taken as the concentration determined at the end of the infusion period for each drug. For each drug, the area under the plasma concentration-time curve at steady state ($[AUC_{24}^{ss}]$ for gefitinib, and from time 0 to time of the last quantifiable concentration $[AUC_{(0\text{-}t)}]$ for vinorelbine and cisplatin) was calculated using the linear trapezoidal rule.

Efficacy

Tumor response was evaluated according to Response Evaluation Criteria in Solid Tumors. Patients continuing to show evidence of response or clinical benefit after completing the six cycles of combination treatment could continue gefitinib monotherapy as part of the trial protocol.

RESULTS

Patients

A total of 23 patients with advanced NSCLC were recruited in five centers in France and Canada between October of 2001 and August of 2002. All patients had measurable disease at baseline in accordance with Response Evaluation Criteria in Solid Tumors. Patient demographic information and key baseline disease characteristics are summarized by dose group (Table 1). The median age was 59 years (range, 24–75), and the majority of patients were PS 0 (60.9%) and had stage IV disease (95.7%). Adenocarcinoma (52.2%) was the most common histology type. Three patients had undergone a previous operation, and two had received radiotherapy for brain metastasis or brain and bony metastases, respectively. Overall, patients in the gefitinib 250-mg group in group B were younger and heavier and had a better PS compared with the other treatment groups.

Treatment

All 23 patients who entered the trial received gefitinib concurrently with at least one cycle of chemotherapy. The mean number of cycles received was 2.3 in group A and 4.6 in group B. A trial flow schema showing patient numbers is

TABLE 1. Baseline Demographics

Patients, no.	23
Group A: gefitinib 250 mg	6
Group B: gefitinib 250 mg	8
Group B: gefitinib 500 mg	9
Age, yr (range)	59 (24–75)
Female:male, no.	10:13
World Health Organization PS 0/1, no.	14/9
Disease stage IIIB/IV, no.	1/22
Histology type, no. (%)	
Adenocarcinoma	12 (52.2)
Large cell	6 (26.1)
Squamous cell	3 (13.0)
Undifferentiated	2 (8.7)
Metastatic sites, no. (%)	
Adrenal	4 (17.4)
Bone	9 (39.1)
Lymph nodes	3 (13.0)
Lung (other than primary tumor)	14 (60.9)
Skin/soft tissue	2 (8.7)
Liver	4 (17.4)
Brain	2 (8.7)
Renal	1 (4.3)

PS, performance status.

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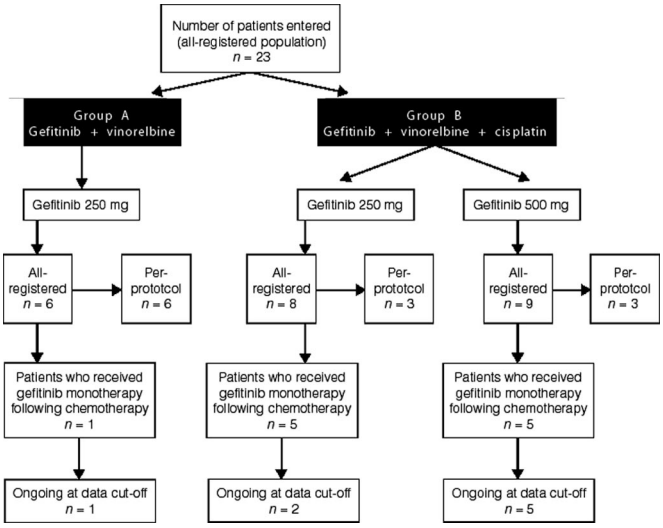

FIGURE 1. Flow diagram of the clinical trial.

illustrated in Figure 1. Eleven patients remained in the trial for ≥6 months and 10 patients for <3 months: eight patients were ongoing at the time of the data cutoff (January of 2003).

In the gefitinib plus vinorelbine single-drug chemotherapy arm, no patients entered the 500-mg dose level: a review of the data from the present trial and a concurrent study[17] indicated an unexpectedly high number of hematologic events (febrile neutropenia and grade 3/4 neutropenia) than would have been anticipated with single-agent vinorelbine. After discussing these data, a decision was made not to escalate the dose to 500 mg.

Dose Reductions/Delays

Nineteen patients (six in group A, five receiving gefitinib 250 mg/day in group B, and eight receiving gefitinib 500 mg/day in group B) had either a dose reduction or cycle delay of vinorelbine due to typical events that were considered to be chemotherapy related, including febrile neutropenia, neutropenia (grade 3/4), anemia, and weight loss.

Thirteen patients (five patients receiving gefitinib 250 mg/day and eight patients receiving gefitinib 500 mg/day in group B) had either a dose reduction or cycle delay of cisplatin due to chemotherapy-related events, including febrile neutropenia, neutropenia, nausea, weight loss, and reduced creatinine clearance. Thirteen patients had one or more interruptions to their gefitinib therapy due to toxicity: four patients in group A, two of whom had two interruptions each (esophagitis [one event], febrile neutropenia [three events], diarrhea [one event] and unidentified toxicities [one event]); three patients in gefitinib 250-mg group B (increased aminotransferases [one event], diarrhea, asthenia, skin rash, and anemia [one event], and acne [one event]); and six patients in gefitinib 500-mg group B (neutropenia [three events], diarrhea [two events], febrile neutropenia [two events, one with concomitant hyponatremia], acne and gastritis [one event]).

Tolerability

DLT

Two patients experienced protocol-defined DLT. In group A, one patient experienced a fatal occurrence of grade 4 febrile neutropenia 3 days after the last vinorelbine administration and after 24 days of gefitinib 250 mg/day treatment. In the gefitinib 500-mg group in group B, one patient experienced grade 3 skin toxicity after 20 days of gefitinib treatment.

AEs

In the combination period, the most common AEs overall (≥15% in any treatment group) included diarrhea, febrile neutropenia, neutropenia, asthenia, stomatitis, anemia, and rash (Table 2). Events that were part of the chemotherapy toxicity profile included asthenia, fever, nausea, vomiting, constipation, and hematologic toxicity. During the gefitinib monotherapy period, grade 1 or 2 diarrhea was the most frequently occurring AE (one and two patients in the 250- and 500-mg dose groups in group B, respectively). There were no serious AEs, withdrawals due to AEs, CTC grade 3 or 4 AEs, or deaths due to AEs during the monotherapy period.

The frequency of common events was generally similar between the two chemotherapy regimens and the two dose groups in group B. A total of 21 patients had grade 3 or 4 AEs during the combination period of this trial: six in group A, six in the 250-mg dose group in group B and nine in the 500-mg dose group in group B (Table 3). The most frequently reported grade 3 AEs during the combination period were febrile neutropenia, anemia, and neutropenia. CTC grade 4 AEs included asthenia, chest pain, mucositis, neutropenia, and febrile neutropenia. With the exception of febrile neutropenia and neutropenia, none of the grade 4 AEs were reported by more than one patient.

Grade 3 or 4 neutropenia affected four of six patients in group A. There was a higher incidence (>50%) of grade 3/4 febrile neutropenia and neutropenia in group A and in the gefitinib 500-mg group in group B compared with the gefitinib 250-mg group in group B, although, based on the small number of patients involved, no robust conclusions on frequency can be drawn. The majority of hematologic AEs were not considered to be related to gefitinib therapy, and there were none during the monotherapy period. Laboratory data supported this overall finding on neutropenia: >62% of patients in each of the treatment groups had a four-grade worsening of their absolute neutrophil count during the study.

Withdrawals

The overall withdrawal rate was 65.2% (15 of 23 patients). Withdrawal rates by treatment group were 83.3% (five of six patients) in group A (gefitinib 250 mg); 75.0% (six of eight) in group B (gefitinib 250 mg); 44.4% (four of nine) in group B (gefitinib 500 mg). The most common reason for withdrawal was disease progression, with 33.3% of patients (gefitinib 250 mg) in group A and 75.0% (gefitinib 250 mg) and 33.3% (gefitinib 500 mg) in group B. AEs accounted for only one withdrawal: grade 3 pneumonitis in a

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TABLE 2. Adverse Events with an Overall Incidence of ≥15% during the Combination Period

	Group A	Group B		All Patients (n = 23)
	Gefitinib 250 mg + Vinorelbine(n = 6)	Gefitinib 250 mg + Vinorelbine + Cisplatin (n = 8)	Gefitinib 500 mg + Vinorelbine + Cisplatin (n = 9)	No. (%)
Diarrhea	4	7	8	19 (82.6)
Neutropenia	4	4	8	16 (69.6)
Asthenia	3	5	6	14 (60.9)
Anaemia	3	5	4	12 (52.2)
Febrile neutropenia	4	2	6	12 (52.2)
Stomatitis	4	5	3	12 (52.2)
Rash	2	4	5	11 (47.8)
Fever	2	5	3	10 (43.5)
Nausea	0	5	5	10 (43.5)
Constipation	1	5	3	9 (39.1)
Vomiting	1	4	3	8 (34.8)
Weight loss	3	2	2	7 (30.4)
Anorexia	3	2	1	6 (26.1)
Chest pain	0	1	4	5 (21.7)
Abdominal pain	1	2	1	4 (17.4)
Hypokalemia	1	0	3	4 (17.4)
Insomnia	1	1	2	4 (17.4)

TABLE 3. Common Toxicity Criteria Grade 3 (or 4 If Indicated) Adverse Events Occurring in at Least One Patient during the Combination Period: All Patients Entered into Trial

		Group A	Group B	
Body System	COSTART Term	Gefitinib 250 mg (n = 6)	Gefitinib 250 mg (n = 8)	Gefitinib 500 mg (n = 9)
Whole body	Asthenia*	1/0	0/0	2/1
Cardiovascular	Pulmonary embolus	0	1	1
Digestive	Diarrhea	1	1	0
Hemic and lymphatic	Neutropenia*	1/3	1/3	2/4
	Febrile neutropenia*	3/1	2/0	4/2
	Anaemia	2	2	3
Metabolic and nutritional	Hypokalemia*	0/1	0/0	2/0

*Grade 3/4.

patient taking gefitinib 500 mg in group B that was considered to be due to both gefitinib and chemotherapy.

A total of 11 patients died during the trial, 10 because of progression of NSCLC. One patient in group A died as a consequence of febrile neutropenia that was judged to be treatment related and therefore qualified as a DLT.

Pharmacokinetics

Effect of gefitinib on exposure to vinorelbine.

For gefitinib plus vinorelbine plus cisplatin (group B), the geometric mean (gmean) $AUC_{(0\text{-}t)}$ for vinorelbine was 10% higher in the presence of steady-state levels of gefitinib 250 mg compared with chemotherapy alone and 14% higher with gefitinib 500 mg (Table 4). The gmean vinorelbine C_{max} was 18% and 6% higher for the 250 mg and 500 mg dose levels, respectively. For group A (gefitinib 250 mg plus vinorelbine), the gmean $AUC_{(0\text{-}t)}$ and C_{max} for vinorelbine were 16% and 50% lower, respectively, in the presence of steady-state levels of gefitinib when compared with the chemotherapy alone (Table 4).

Comparison of individual $AUC_{(0\text{-}t)}$ ratios suggested that there was no tendency toward either a lower or higher exposure to vinorelbine, irrespective of treatment arm or gefitinib dose level. Individual C_{max} ratios showed similar results (Table 4). For vinorelbine alone, the population intra-individual variation equates to mean individual ratios ranging from 0.60 to 1.67. Hence, there would appear to be no effect on exposure to vinorelbine when it is given either alone or with cisplatin in the presence of steady-state levels of gefitinib.

Effect of chemotherapy on exposure to gefitinib.

No patient exceeded the twofold intrasubject variability exposure to gefitinib and comparison of individual $AUC_{(0\text{-}t)}$

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TABLE 4. Plasma Pharmacokinetic Parameters of Vinorelbine Alone and in Combination with Gefitinib: All Assessable Patients Entered into the Trial

		Group A		Group B			
Parameter (Units)	**Summary Statistics**	**Gefitinib 250 mg**	**+ Vinorelbine**	**Gefitinib 250 mg**	**+ Vinorelbine and Cisplatin**	**Gefitinib 500 mg**	**+ Vinorelbine and Cisplatin**
Patients, no.		5	5	6	6	6	6
C_{max}, ng/mL	gmean (CV%)	13.1 (81.0)	6.9 (45.7))	11.0 (108)	13.0 (64.4)	15.4 (43.3)	16.4 62.4)
$AUC_{(0-t)}$, ng/hr/mL	gmean CV%)	9.0 24.4)	7.5 57.0)	7.9 34.7)	8.7 35.1)	10.8 33.2)	12.3 42.6)
Individual ratios of $AUC_{(0-t)}$ with and without gefitinib, range		0.40–1.60		0.67–1.78		0.52–1.27	

C_{max}, maximum plasma concentration; gmean, geometric mean; CV, coefficient of variation; $AUC_{(0-t)}$, area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration.

ratios suggested that there was no evidence of a shift to a higher or lower steady-state exposure to gefitinib when in combination with vinorelbine or vinorelbine/cisplatin (Table 5). Hence, there would appear to be no effect on steady-state exposure to gefitinib when it is given with either vinorelbine alone or with the vinorelbine/cisplatin combination.

Effect of gefitinib on exposure to cisplatin.

Because of stability problems relating to the preparation of plasma ultrafiltrate, data from only six patients were available. Although the intrapatient variability for cisplatin is not known, comparison of individual $AUC_{(0-t)}$ ratios suggested that there was no shift to a higher or lower exposure to cisplatin when it was given in combination (Table 6). Thus, from this limited data set, there would appear to be no effect on exposure to cisplatin when given with vinorelbine in the presence of steady-state levels of gefitinib.

Efficacy

Five patients (21.7%) had a confirmed partial response for ≥3 months, including two who had responses that were maintained for ≥6 months. An additional six patients had stable disease, giving 11 patients with disease control (partial response plus stable disease), nine of whom had disease control for >3 months (Table 7). Five patients (21.7%) progressed, and seven were not assessable for tumor response (Table 7). Median survival for patients receiving gefitinib 250 mg/vinorelbine in group A was 2.8 months (95% confidence interval [CI], 1.3–3.0); for patients receiving gefitinib 250 mg/vinorelbine plus cisplatin in group B, median survival was 9.9 months (95% CI, 4.7, upper limit not calculable due to insufficient events). Median progression-free survival for patients receiving gefitinib 250 mg/vinorelbine (group A) was 1.5 months (95% CI, 1.3–1.8), and for patients receiving gefitinib 250 mg/vinorelbine plus cisplatin (group B), it was 6.1 months (95% CI, 1.4, upper limit not calculable due to insufficient events). Median survival and progression-free survival for patients receiving gefitinib 500 mg in group B were not calculable due to insufficient events.

DISCUSSION

Overall, the safety data from this trial are consistent with previously conducted trials with gefitinib that showed a higher incidence of AEs with 500 mg/day compared with 250 mg/day. The majority of the commonly reported gefitinib-related AEs in this study, e.g., rash and diarrhea, were consistent with those reported in other trials and with the AE profile seen in trials of gefitinib monotherapy.[6,7] Indeed, during the gefitinib monotherapy period, grade 1 or 2 diarrhea

TABLE 5. Pharmacokinetic Parameters for Gefitinib Given Alone and in Combination with Vinorelbine or Vinorelbine plus Cisplatin: All Assessable Patients Entered into the Trial

		Group A		Group B			
Parameter (Units)	**Summary Statistics**	**Gefitinib 250 mg**	**+ Vinorelbine**	**Gefitinib 250 mg**	**+ Vinorelbine and Cisplatin**	**Gefitinib 500 mg**	**+ Vinorelbine and Cisplatin**
Patients, no.		5	5	7	7	6	6
$C_{min}{}^{ss}$, ng/mL	gmean (CV%)	418 33.7)	478 35.1)	231 42.1)	205 39.6)	283 78.6)	269 79.7)
$AUC_{24}{}^{ss}$, ng/hr/mL	gmean CV%)	11900 48.4)	13400 32.3)	7240 29.0)	7330 25.9)	8610 70.8)	9180 61.1)
Individual ratios of $AUC_{24}{}^{ss}$ with and without vinorelbine (range)		0.83–1.94		0.76–1.32		0.93–1.40	

$C_{min}{}^{ss}$, minimum (trough) steady-state plasma concentration during the 24-hour dosing interval; gmean, geometric mean; CV, coefficient of variation; $AUC_{24}{}^{ss}$, area under the plasma concentration-time curve at steady state.

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TABLE 6. Pharmacokinetic Parameters of Free Platinum (ng/mL)

Parameter (Units)	Summary Statistics	Gefitinib 250 mg		Gefitinib 500 mg	
		Cisplatin	Cisplatin + Gefitinib 250 mg	Cisplatin	Cisplatin + Gefitinib 500 mg
Patients, no.		3	3	3	3
C_{max}, ng/mL	gmean (CV%)	1900 39.0)	1410 16.8)	1360 14.4)	1330 50.8)
$AUC_{(0-t)}$, ng/hr/mL	gmean CV%)	3120 39.2)	2510 15.1)	2300 7.44)	2260 48.0)
Individual ratios of free platinum $AUC_{(0-t)}$ with and without gefitinib			0.47 0.82 1.35		0.58 1.25 1.31

C_{max}, maximum plasma concentration; gmean, geometric mean; CV, coefficient of variation; $AUC_{(0-t)}$, area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration.

TABLE 7. Patients Experiencing Tumor Response, Stable Disease, or Disease Progression

Best Overall Response	Group A	Group B		
	Gefitinib 250 mg/day (n = 6)	Gefitinib 250 mg/day (n = 8)	Gefitinib 500 mg/day (n = 9)	All Patients (n = 23)
Partial response, no. (%)	1 (16.7)	3 (37.5)	1 (11.1)	5 (21.7)
Stable disease, no. %)	0	2 (25.0)	4 (44.4)	6 (26.1)
Disease progression, no. %)	2 (33.3)	2 (25.0)	1 (11.1)	5 (21.7)
Not assessable, no. %)	3 (50.0)	1 (12.5)	3 (33.3)	7 (30.4)

was the most frequently occurring AE (one and two patients in the 250- and 500-mg dose groups in group B, respectively). However, with the combinations studied here, there was a higher than expected incidence of hematologic AEs, specifically febrile neutropenia and grade 3/4 neutropenia. This unexpected and unacceptably high toxicity did not seem to be related to a gefitinib-mediated drug interaction because pharmacokinetic data demonstrated no effect on steady-state exposure to gefitinib when given with chemotherapy or on exposure to vinorelbine, given with or without cisplatin, in the presence of steady-state levels of gefitinib. In INTACT (IRESSA NSCLC Trial Assessing Combination Treatment) 1, the combination of gefitinib, cisplatin, and gemcitabine showed no unexpected AEs.[11] Recurrent febrile neutropenia and neutropenia in the present study may have been exacerbated by chemotherapy dose reductions that were not always followed as outlined in the protocol. In addition, some patients had their dose reduced and then subsequently reescalated.

A planned phase II part of this trial did not proceed for two main reasons. First, the combination of gefitinib and vinorelbine was associated with unacceptable hematologic toxicity in this trial and in a second trial involving gefitinib/vinorelbine combination therapy, in which 72% of patients experienced grade 3/4 neutropenia and three treatment-related deaths were recorded.[17] Second, data from the INTACT 1 and 2 phase III trials showed that the addition of gefitinib 250 or 500 mg to the standard doublet chemotherapies gemcitabine/cisplatin or carboplatin/paclitaxel did not confer a statistically or clinically significant survival advantage compared with a placebo/chemotherapy regimen in patients with advanced NSCLC.

Based on these small numbers of patients, within-patient data comparisons suggest that there was no pharmacokinetic interaction between cisplatin and gefitinib at either gefitinib dose level. This result is consistent with an earlier gefitinib combination study that investigated the potential for a pharmacokinetic interaction with cisplatin when given as the gemcitabine/cisplatin combination.[10] Similarly, there was no apparent pharmacokinetic interaction between gefitinib and vinorelbine. This combination was the most likely source of any interaction based on the possibility of CYP3A4 substrate competition. The lack of interaction confirms the results of an in vitro study of the potential for a competitive inhibition effect on CYP3A4 between gefitinib and vinorelbine that concluded that no drug-drug interaction would occur in vivo when these two agents were combined.[18]

Antitumor activity was observed in both groups. A greater number of patients receiving gefitinib 250 mg plus vinorelbine/cisplatin (group B) had stable disease than those patients receiving gefitinib 250 mg plus vinorelbine alone (group A), although it is difficult to draw firm efficacy conclusions for the different regimens due to the small patient numbers in the treatment groups.

Research is warranted to identify the exact reason for potentiation of vinorelbine myelosuppression when delivered in patient receiving gefitinib. A possible explanation would be gefitinib-induced cytochrome P-450 (CYP3A4) activity, an enzyme responsible for the metabolism of a wide variety of chemicals, including anticancer agents. Induction of

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CYP3A4 by gefitinib has been suggested by a study demonstrating that urinary 6β-hydroxycortisol level, a cortisol metabolite correlated with CYP3A4 activity, increased in patients receiving gefitinib.[19] The cytochrome P-450 system catalyzes the rate-limiting step in the overall metabolism and subsequent elimination of many drugs and is known to be involved in the metabolism of many anticancer drugs such as vinca-alkaloid including vinblastine, vincristine, and vinorelbine.[20]

In conclusion, despite positive efficacy and pharmacokinetic data, the combination of gefitinib with vinorelbine alone or with vinorelbine plus cisplatin cannot be considered acceptable due to a high incidence of hematologic toxicity, specifically CTC grade 3/4 neutropenia and febrile neutropenia. Unexpected myelotoxicity with the combination of gefitinib and vinorelbine has also been reported in a small study in Japanese patients.[21] These data illustrate that it is not possible to assume that because a new drug may be safely combined with certain standard chemotherapy regimens (e.g., carboplatin/paclitaxel or cisplatin/gemcitabine in the case of gefitinib) that it is safe to extrapolate results and combine the agent with other regimens outside a clinical trial.

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